REMARKS

Statement of the Substance of the Interview

Applicants' representatives thank Examiner Eileen O'Hara for the courtesy extended during the interview on April 13, 2006. At the interview, Applicants discussed why the present application is entitled to the priority date of January 14, 1997 on the basis that the 60/035,496 application disclosed a specific substantial and credible utility satisfying the requirements of 35 U.S.C. § 101. Applicants also discussed that Applicants' identification and disclosure of the conserved cysteine rich domain of TNFR-6α, could be used to respond to the written description rejection under 35 U.S.C. § 112, first paragraph. The remarks herein are made in accordance with our discussion during the interview.

Status of the Claims

Upon entry of the present amendment, claims 24-46, 51-61 and 66-88 will be pending. Claims 47-50, 62-65, 102-116 and 124-131 have been cancelled without prejudice or disclaimer. Cumulatively claims 1-23, 47-50, 62-65 and 89-131 have been cancelled. Applicants reserve the right to pursue the subject matter of the cancelled claims in one or more continuing or divisional applications.

Claims 46 and 61 have been amended to replace "90% or more identical" with "95% or more identical." Support for this amendment may be found in the specification as filed, for example at page 7, line 12 to page 8, line 7. Accordingly, no new matter has been added and Applicants respectfully request these amendments be entered.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 46-75, 102-116, and 124-125 stand rejected under 35 U.S.C. §112, first paragraph for allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner stated that,

> "There is no identification of any particular portion of the structure that must be conserved in order to conserve the required function. Clearly, such does not constitute

> disclosure of a representative number of examples of, nor adequate written description for, the claimed genus." (See, Office Action mailed January 24, 2006 at page 3, lines 12-15.)

Applicants respectfully disagree.

Preliminarily, Applicants note that claims 47-50, 62-65, 102-116, 124-125 and claims dependent therefrom have been cancelled. Accordingly, this rejection insofar as it applies to claims 47-50, 62-65, 102-116, 124-125 has been obviated or overcome. Moreover Applicants note that claims 46 and 61 have been amended to replace "90% or more identical" with "95% or more identical."

Applicants direct the Examiners' attention to the disclosure at page 4, lines 3-5, which indicates that TNF receptor family members are "defined by the presence of cysteine-rich repeats in their extracellular domains." This conserved cysteine rich domain was known, as of the earliest priority date of the application, to be involved in ligand binding. (See, e.g., Gruss and Dower, Blood 85:3378, cited as reference DP on the Revised Form PTO/SB/08 submitted herewith, which states in the sentence bridging the two columns on page 3378 that, "These receptor superfamily is characterized by multiple cysteine rich domains in the extracellular (amino-terminal) domain, which have been shown to be involved in ligand binding.") The cysteine rich domain TNFR-6α (SEQ ID NO:2) is clearly identified in the specification. At page 13, lines 18-20, it is disclosed that, "Importantly, these proteins [TNFR-6α, TNFR-6β and TNFR-2] share substantial sequence similarity over their extracellular domains including four repeated cysteine rich motifs with significant intersubunit homology." Further, at page 100, lines 8-12, it is disclosed that because TNFR-6α is a member "of the TNF receptor-related protein family, to modulate rather than completely eliminate biological activities of TNFR preferably mutations are made in sequences encoding amino acids in the TNFR conserved extracellular domain, more preferably in residues within this region which are not conserved among members of the TNF receptor family." Figure 4 shows an alignment of 12 known TNFR proteins with the proteins disclosed in the application. One skilled in the art could easily identify the conserved cysteine residues which are found in nearly every member of the TNFR family, with the first conserved cysteine in TNFR-6α being located at amino acid 49 and the last conserved cysteine residues being located at amino acid 193. At page 79, lines 7-10, the specification teaches that amino acid 49 is the position of the

first cysteine residue from the N terminus of the complete TNFR-6α and TNFR-6β polypeptides...believed to be required for activity of the TNFR-6α and TNFR-6β proteins." Likewise, it is indicated at page 83, lines 16-21, that polypeptides having further C terminal deletions including the "cysteines at positions 193 and 132 of SEQ ID NOS:2 and 4, respectively, would not be expected to retain such biological activities because it is known that these residues in TNF receptor-related polypeptides are required for forming disulfide bridges to provide structural stability which is needed for receptor binding." Accordingly, the present application clearly discloses that the region between amino acids 49 and 193 contain the conserved cysteine rich domain of TNFR-6α which is critical to TNFR-6α function.

Applicants note that rejected claims 46 and 61, claim polypeptides that are at least 95% (as amended herein) or more identical to regions of TNFR-6α (SEQ ID NO:2) comprising the entirety of the conserved cysteine rich domain region. In view of the foregoing, Applicants submit that the specification clearly discloses the region of amino acids 49-193 of SEQ ID NO:2 as being critical for function and that therefore, the disclosure provides adequate written description of the claimed genus. Applicants believe the present rejection has been obviated or overcome and respectfully request that this rejection be reconsidered and withdrawn.

Entitlement to Priority

The Examiner maintains the position that the present application is not entitled to receive the benefits of priority under 35 U.S.C. §§ 120 or 119(e) with respect to the 09/006,352 and 60/035,496 applications because these applications allegedly do not disclose a specific and substantial utility. Thus, the Examiner has accorded the present application an effective filing date of March 4, 1999.

Applicants respectfully disagree and traverse.

Previously, Applicants asserted that the 60/035,496 application discloses a utility fulfilling the requirements 35 U.S.C. §§ 120 or 119(e) by virtue of its disclosure that TNFR-6α (SEQ ID NO:2) may be used in the treatment of graft versus host disease. Applicants demonstrated that the asserted utility had been confirmed by Zhang et al.,

Journal of Clinical Investigation 107:1459 (2001), who showed that TR6-Fc[1] treatment reduces symptoms in a murine model of graft vs. host disease. Applicants also argued that the asserted utility was a specific, substantial and credible utility as defined in the current United States Patent and Trademark Office's Utility Guidelines.

The Examiner was not persuaded by Applicants arguments and, in particular, held that the asserted utility was credible, but not specific and substantial. (see, Office Action mailed November 4, 2005 at page 3, lines 12-13.) In support of the rejection, The Examiner stated that,

> "graft versus host disease was one of many different diseases or disorders asserted to be treatable with the protein of the instant invention (60/035,496, page 7), and are all diseases or disorders known to involve cytokines and receptors in the TNF family....Therefore while asserted utility was credible in the earlier applications, it was not specific and substantial." (see, Office Action mailed January 24, 2006 at page 4, line 17 to page 5, line 2.)

Applicants respectfully disagree.

As Applicants' primary response, Applicants maintain that the use of the polypeptide of SEQ ID NO:2 in the treatment of graft versus host disease is a disclosed utility for the claimed invention that satisfies the requirement for patentable utility under 35 U.S.C. § 101. Second, the fact that Applicants have disclosed more than one utility for the polypeptide does not negate the fact that the utility requirement has been met. Applicants will also provide evidence that the listed diseases in the application are inter-related and several of the listed diseases can be asserted to satisfy the utility requirement of 35 U.S.C. §101.

Use of the polypeptide of SEQ ID NO:2 in the treatment of graft versus host disease is a patentable utility.

The Examiner particularly rejected Applicants' asserted utility because it allegedly was not "specific and substantial."

M.P.E.P. § 2107.02 defines a "specific utility" as one that "is *specific* to the subject matter claimed." M.P.E.P. § 2107.02 further goes on to state that a specific utility

[1] Full-length human TR6 in Zhang et al. is the same as TNFR6-alpha (SEQ ID NO:2) of the present application.

"contrasts with a *general* utility that would be applicable to the broad class of the invention." By way of illustration, the M.P.E.P indicates that use of a polynucleotide as a "gene probe" or "chromosome marker" is a general utility as is the assertion that a compound is useful in "treating unspecified disorders." A "substantial utility" is defined by the M.P.E.P as one that "defines a 'real world' use." M.P.E.P. § 2107.02 further indicates that "a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a 'substantial utility' define a 'real world' context of use."

Certainly, the asserted utility in this case, treatment of graft versus host disease, is a specific utility because it is not a utility that is applicable to the broad class of the invention; not all polypeptides can be used to treat graft versus host disease. Additionally, the asserted utility is a substantial utility because a method of treating graft versus host disease certainly is a "real world" use with "immediate benefit to the public." Thus, Applicants submit that the asserted utility is sufficient under all applicable authority to satisfy the utility requirement set forth in 35 U.S.C. § 101.

Disclosure of more than one utility for the polypeptide does not negate the fact that the utility requirement has been met.

In response to the Examiner's contention that the asserted utility is not adequate because the application lists multiple utilities, Applicants point out that is a common and accepted practice to disclose several utilities for an invention. Further, all that is required to meet the utility requirement is that there be one adequate assertion of utility to meet the utility requirement of 35 U.S.C. § 101. Additional assertions of utility, *even if incredible*, do not render the claimed invention lacking in utility. This is set forth in M.P.E.P., 8th Edition, Revision 3 at § 2107.02:

> It is common and sensible for an applicant to identify several specific utilities for an invention, particularly where the invention is a product (e.g., a machine, an article of manufacture or a composition of matter). However, regardless of the category of invention that is claimed (e.g., product or process), an applicant need only make one credible assertion of specific utility for the claimed invention to satisfy 35 U.S.C. 101 and 35 U.S.C. 112; ***additional statements of utility, even if not "credible," do not render the claimed invention lacking in utility.*** See, e.g., *Raytheon v. Roper*, 724 F.2d 951, 958, 220 USPQ 592, 598 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 835 (1984) ("When a properly claimed invention meets at least one stated objective, utility under

> 35 U.S.C. 101 is clearly shown."); *In re Gottlieb*, 328 F.2d 1016, 1019, 140 USPQ 665, 668 (CCPA 1964) ("Having found that the antibiotic is useful for some purpose, it becomes unnecessary to decide whether it is in fact useful for the other purposes 'indicated' in the specification as possibly useful."); *In re Malachowski*, 530 F.2d 1402, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988). ***Thus, if applicant makes one credible assertion of utility, utility for the claimed invention as a whole is established.*** (See, M.P.E.P., 8th Edition, Revision 3, §2107.02, paragraph bridging columns on page 2100-37, emphasis added)

Thus, Applicants maintain that disclosure of the use of the claimed polypeptides in the treatment of graft versus host disease is sufficient to meet the utility requirement of 35 U.S.C. § 101, regardless of whether or not additional disclosed utilities in the application also fulfill the utility requirement of 35 U.S.C. § 101.

The listed diseases in the application are inter-related and several of the listed diseases can be asserted to satisfy the utility requirement of 35 U.S.C. §101.

The specification of the 60/035,496 application, the earliest priority application of the present application discloses that

> The invention also provides for pharmaceutical compositions comprising TNFR polypeptides, particularly human TNFR polypeptides, which may be employed, for instance, to treat infectious disease including HIV infection, endotoxic shock, cancer, autoimmune diseases, graft vs. host disease, acute graft rejection, chronic graft rejection, neurodegenerative disorders, myelodysplastic syndromes, ischemic injury, toxin-induced liver disease, septic shock, cachexia and anorexia. (See, 60/035,496 application at page 7, lines 14-20)

This disclosure carries through all of the priority disclosures to the present application. The same disclosure may be found in the 09/006,352 application at page 6, lines 26-32; and in the present application at page 8, line 28 to page 9, line 6.

Applicants note that the listed diseases are not a disparate and unrelated set of diseases. Instead, as the Examiner acknowledged at page 4, line 19-20 of the office action mailed January 24, 2006, the disclosed diseases are inter-related by virtue of the fact they are diseases in which members of the TNF receptor-ligand pairs have been implicated in the pathology. Clearly, this is not a list of diseases for which the general class of proteins compounds would be useful.

Moreover, in addition to graft versus host disease, Applicants can rely on several other assertions of utility from the listed diseases to fulfill the utility requirement of 35 U.S.C. §101. In addition, to being useful in the treatment of graft versus host disease, the polypeptide of SEQ ID NO:2 is also useful, in the treatment of graft rejection, autoimmune disease, infection and HIV. References supporting the use of the polypeptide of SEQ ID NO:2 in each of these diseases are described below. In the art, the polypeptide of SEQ ID NO:2 has been assigned the official nomenclature of tumor necrosis factor receptor superfamily, member 6b (TNFRSF6b). TNFRSF6b is also known by the gene aliases, TR6 and DCR3 as documented in the National Center for Biotechnology's (NCBI) Entrez Gene Report for TNFRSF6b (a copy of which is provided herewith as Exhibit A). An alignment of TNFRSF6b as disclosed in GenBank RefSeq entry NP_003814 (NP_003814 is listed on page 3 of the Entrez Gene report) with the polypeptide of SEQ ID NO:2 is shown as Exhibit B.

1) Graft Rejection: Zhang et al., *Journal of Clinical Investigation* 107:1459 (2001), a copy of which was previously submitted as reference CD listed on the Revised form PTO/SB/08 submitted November 20, 2001. In addition to showing that TR6-Fc treatment reduces symptoms in a murine model of graft vs. host disease, Zhang et al, show that administration of TR6-Fc prolongs heart allograft survival in mice.

2) Autoimmune Disease: Sung et al., *The Journal of Experimental Medicine* 199:1143 (2004), a copy of which is provided herewith as reference DR listed on the Revised Form PTO/SB/O8. Working with non-obese diabetic (NOD) mice, a murine model of autoimmunity in which the animals spontaneously develop autoimmune diabetes, Sung et al. show that transgenic expression of DCR3 protects NOD mice from autoimmune diabetes in a dose dependent fashion.

3) Infection: Matute-Bellow et al, *The Journal of Infectious Disease* 191:596 (2005), a copy of which is provided herewith as reference DQ listed on the Revised Form PTO/SB/O8. Matute-Bellow et al, show that systemic administration of DCR3-a[2] improves the clearance of bacteria from the lungs in

[2] DCR3a is an analogue of TNFRSF6b in which the arginine at position 218 is changed to a glutamine. This mutation stabilizes against proteolytic degradation but does not alter the ability of TNFRSF6b to bind FasL (see Sung et al at page 596, left column, second full paragraph).

mice with pneumococcal pneumonia. At page 603, Matute-Bellow et al. state that "This improvement in clearance of bacteria was associated with decreased weight loss, indicating a better clinical status."

4) HIV: Badley et al., *Journal of Virology* 70:199 (1996), a copy of which is provided herewith as reference DO listed on the Revised Form PTO/SB/08. The disclosure spanning page 168, line 1 to page 169, line 5 of the present specification[3] teaches that HIV-induced apoptosis contributes to the loss of T lymphocytes that results in the state of immunodeficiency that characterizes AIDS. The specification further teaches that TNFR polypeptides may be used to treat HIV+ individuals to reduce selective killing of CD4 lymphocytes." See, page 169, lines 3-5[4] of the specification as filed. Badley et al., show that inhibition of apoptosis with M38, an anti-Fas antibody, inhibits the ability of HIV infected macrophages to induce apoptosis of Jurkat T cells and of human PHA- and IL-2 activated peripheral blood T cells. Accordingly, the use of the protein of SEQ ID NO:2 in the treatment of HIV, is yet another asserted utility that Applicants can rely upon to fulfill the requirements of 35 U.S.C. § 101.

With respect to the assertions that the polypeptide of SEQ ID NO:2 is useful in the treatment of graft versus host disease, graft rejection, autoimmune disease and infection, Applicants remind the Examiner that the Federal Circuit held in *In re Brana*, evidence dated after the filing date "can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification." 51 F. 3d. 1560, 1567 at n19 (Fed. Cir. 1995). Such evidence "goes to prove that the disclosure was in fact enabling when filed (*i.e.*, demonstrated utility)." *Id., citing In re Marzocchi*, 439 F2d. at 224 n.4, 169 U.S.P.Q. at 370 n.4.

With respect to the assertion that the polypeptide of SEQ ID NO:2 is useful in the treatment of HIV, Applicants would also like the Examiner to note that this disease is not

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[3] This disclosure carries through all of the priority disclosures to the present application and may be found in the 09/006,352 application at page 44, lines 4-31; and in the present application at page 168, line 1 to page 169, line 5.

[4] The corresponding disclosure in the 09/006,352 and 60/035,496 applications disclose "a method for treating HIV^+ individuals is provided which involves administering an antagonist of the present invention to reduce selective killing of CD4 T-lymphocytes". Also in those specifications, an antagonist is defined as including "soluble forms of TNFR" (See, the 60/035,496 provisional at page 51, lines 24-26 and 09/006,352 application at page 40 lines 3-5).

only disclosed in the list of diseases on page 8, line 28 to page 9, line 6 (corresponding to lines 14-20 of the 60/035,496 priority application), but is also specifically contemplated as a highlighted disease at page 168, line 1 to page 169, line 5 corresponding to pages 55-56 of the 60/035,496 specification.

Conclusion

Applicants have demonstrated that at least five of the disclosed utilities for the polypeptide of SEQ ID NO:2 can be used to satisfy the utility requirement of 35 U.S.C. § 101. Accordingly, Applicants maintain that the present application is entitled to receive the benefits of priority under 35 U.S.C. §§ 120 or 119(e) with respect to the 09/006,352 and 60/035,496 applications and that the present application should be accorded an effective filing date of January 14, 1997.

Rejections under 35 U.S.C. § 102

The Examiner has rejected claims 24-88 and 102-131 under 35 U.S.C. §102(e), as being anticipated by Ashkenazi et al., U.S. Patent No. 6,764,679 which the Examiner has assigned an effective priority date of September 19, 1998.

As described above, the present application is entitled to a priority date of January 14, 1997 and thus, the Ashkenazi reference, U.S. Patent No. 6,764,679, is not available as prior art under 35 U.S.C. §102 with respect to the present application. Accordingly, Applicants respectfully request that the present rejection be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing remarks, Applicants believe that this application is now in condition for allowance, and an early notice to that effect is urged. The Examiner is invited to call the undersigned at the phone number provided below if any further action by Applicant would expedite the examination of this application.

Finally, if there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for in the Petition for an Extension of Time submitted concurrently herewith, such an extension is requested and the appropriate fee should also be charged to our Deposit Account.

Dated: April 25, 2006

Respectfully submitted,

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